INTRODUCTION

The hypothalamus and pituitary form a functionally integrated complex. The pituitary gland is suspended by the pituitary stalk from the lowermost part of the hypothalamus. There are two parts to this gland: an anterior lobe that is derived embryologically from an evagination of the stomodeum (foregut), known as Rathke’s pouch, and a posterior lobe formed by downward evagination of the brain. The anterior lobe is regulated by chemical factors produced by specialized neurons that terminate in the median eminence of the medial basal hypothalamus. These neurons abut fenestrated capillaries, derived from the arterial system in the anterior circle of Willis, that join to form the hypothalamo-pituitary portal vessels. The portal vessels run down the pituitary stalk to connect with the sinusoidal vessels of the anterior pituitary. In consequence, this system allows the hypothalamic regulatory neurohormones to bathe the pituitary cells (Fig. 15.1).

The chemical nature of the hypothalamic regulatory factors has now been elucidated. Most are peptide releasing factors, but hypothalamic inhibition of PRL secretion is mediated largely by dopamine (Fig. 15.2). Gonadotrophin-releasing hormone (GnRH) is released in a pulsatile manner; indeed, unremitting sustained exposure to GnRH abolishes pituitary LH secretion (Fig. 15.3).

- The posterior pituitary lobe is a storage depot for vasopressin (antidiuretic hormone, or ADH) and oxytocin

The hormones of the posterior lobe are synthesized in the magnocellular neurons of the supraoptic and paraventricular hypothalamic nuclei. They are produced as large precursor molecules that include specific carrier moieties called neurophysins. During axonal passage to the posterior lobe the precursors are cleaved to yield equimolar quantities of the hormones and their carrier neurophysins. Their release is regulated at the hypothalamic level, so hormonal disturbances usually reflect hypothalamic disorder rather than primary pituitary disease.

- The anterior pituitary secretes six major hormones: growth hormone (GH, or somatotrophin), the two gonadotrophins follicle-stimulating hormone (FSH) and luteinizing hormone (LH), thyroid-stimulating hormone (TSH), adrenocorticotrophin (ACTH, or corticotrophin) and prolactin (PRL)
All the hormones of the anterior lobe except PRL act largely through target glands – Including the thyroid, adrenal cortex, gonads and, in the case of GH, the liver, which produces IGF-I (Fig. 15.4). GH also stimulates other organs to produce IGF-I, which acts in a local paracrine fashion.

According to the archaeological records, the diseases of GH excess (gigantism and acromegaly) and deficiency (Fig. 15.5) were known in antiquity. The identification of pituitary tumours preceded the recognition of the endocrine effects. Acromegaly was first clearly described by Pierre Marie a century ago. Harvey Cushing, besides describing the disease named after him, largely developed a safe technique for neurosurgery of the pituitary, including transsphenoidal and transfrontal approaches, and contributed to the physiological understanding of pituitary function in parallel to others performing animal studies on this gland.

Epidemiological studies of the pituitary are incomplete. Small tumours are commonly found here in autopsy studies of people dying suddenly from accidental causes; most are presumably clinically silent though some stain for PRL. The incidence of clinically significant tumours in the developed world is 20–30 per million per year. Their presentation depends on geography and economics. In Africa the commonest presentation is blindness from a large

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**Fig. 15.1 Hypothalamo-anterior pituitary neurovascular link.**

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Hypothalamic releasing/inhibitory factors and anterior pituitary hormone responses

Fig. 15.2 Hypothalamic releasing/inhibitory factors and anterior pituitary hormone responses.

Tonic secretion of pituitary gonadotrophin

Fig. 15.3 Differential influence of pulsatile versus sustained GnRH administration on LH release (modified from Belchetz et al. 1978 Science 202: 631–633, with permission).
Growth hormone actions

Fig. 15.4  GH action largely mediated by IGF-I.

Fig. 15.5  Skeleton of GH-deficient adult compared with normal-sized skeleton; both were excavated from the same Roman graveyard.
tumour compressing the optic pathways. However, most tumours are functionless and present with features of a space-occupying lesion with various degrees of hypopituitarism. The recognition of hypersecreting lesions, especially GH and PRL and less frequently ACTH, gonadotrophins and TSH, follows from extra features that are detailed below. The impact of these disorders on mortality and morbidity is increasingly being recognized and defined.

- Acromegaly is estimated to have an incidence of 4–6 new cases per million per year with a prevalence of approximately 40 per million. Overall mortality is twice normal but is reduced to near normal in patients treated so that their mean GH averages less than 5 mU/L (2.5 ng/ml). The major causes of death are cardiovascular, respiratory and cerebrovascular. There is an increased incidence and mortality from colonic cancer.

### PATHOGENESIS AND PATHOLOGY

#### PITUITARY TUMOURS

Pituitary tumours are rarely part of multiple endocrine neoplasia, type 1 (MEN-1) syndrome, which may be familial (see Ch. 23). The tumour suppressor gene for this syndrome located on chromosome 11 has been cloned and its common mutations resulting in MEN-1 have been identified. A constitutively active mutation of the stimulatory G protein (gsp) has been postulated as the cause of GH-secreting adenomas in up to 40% of cases. Rare familial cases of acromegaly have been recorded but so far the genetic abnormality has not been identified in non-MEN-1 cases. Aggressive tumours of the pituitary have been associated with abnormalities in a number of oncogenes and tumour suppressor genes (Fig. 15.6). It has long been noted that in many cases of Cushing’s disease either no discrete lesion can be found at surgery or diffuse hyperplastic changes are noted. The blunted rather than fully resistant suppression of cortisol production following dexamethasone administration, the exuberant ACTH response to exogenous corticotrophin-releasing hormone (CRH, also called ACTH-releasing factor) and desmopressin together with the pathological features prompted early ideas that hypothalamic secretion might be responsible. There are alternative explanations, however, such as constitutive activation in the pituitary receptors for releasing factors. Transgenic mice overexpressing the GHRH (GH-releasing hormone) gene display initial hyperplasia before developing tumours of somatroph cells. Also, most pituitary tumours studied are monoclonal, which suggests there is true neoplastic transformation.

The pathological characterization of pituitary tumours is based on classical haematoxylin and eosin staining and subsequent trichrome variants. There are three major categories:

**Classification of pituitary tumours**

- Chromophobe, often functionless tumours (Fig. 15.7a)
- Eosinophilic, often producing GH or PRL (Fig. 15.7b)
- Basophilic, particularly associated with Cushing’s disease (Fig. 15.76c)
Sensitive and specific immunostaining techniques reveal the existence of gonadotrophin- and TSH-secreting tumours, oncocytic tumours and functionless tumours staining for synaptophysin and chromogranin. Immunostaining features do not invariably correlate with secretory activity, however.

### Fig. 15.7 Histopathological classification of pituitary tumours according to haematoxylin and eosin staining: (a) chromophobe, (b) eosinophilic and (c) basophilic.

### Oncogenes and tumour suppressor genes possibly related to pituitary tumorigenesis

#### Oncogenes

- **Gs**
  - Mutations in G, protein: 201 Arg → Cys/His or 227Gln → Arg/Leu ? 40% GH secreting adenomas in Caucasian patients, fewer in Japanese
- **CREB**
  - ? facilitating role in somatotroph transformation and GH gene transcription
- **RAS**
  - Found in metastases from pituitary carcinomas and aggressive prolactinoma
- **PTTG**
  - Increased expression in many types, greater expression with more invasive tumours

#### Tumour suppressor genes

- **9p**
  - Early change in non-functional tumours, rare in somatotrophinomas
- **9p21**
  - Early change as above, via protein p16, interfering with cell cycle
- **13q**
- **10q23**
  - Transition to invasive/metastatic phenotype, in all subtypes or pituitary tumour
- **11q13**
  - As above: via menin? closely situated gene product
- **12p13**
  - As above via p27? post-translational action on cell cycle regulation
- **13q**
  - As above: all subtypes
- **17p**
  - Via p53 as above, all subtypes
- **17p21**
  - Via m23 as above, all subtypes
The invasiveness of pituitary tumours varies greatly, but as with many endocrine tumours this characteristic correlates only poorly with observed features such as mitotic figures or nuclear pleomorphism. Dural invasion is often difficult to recognize at surgery but is commonly the cause of recurrence. Pituitary carcinomas are extremely rare but examples are documented both for PRL-, GH-, ACTH- or TSH-secreting and for endocrinologically functionless tumours. They are defined by the presence of distant metastases within, or much more rarely outside, the CNS.

OTHER HYPOTHALAMO–PITUITARY DISORDERS

For other pathologies in the hypothalamus-pituitary region a number of tests are appropriate:

- **Cranioopharyngioma**
  The presence of calcified cysts containing β-hCG (beta human chorionic gonadotrophin)

- **Lymphocytic hypophysitis**
  Lymphocytes for cd4 (cluster of differentiation 4)

- **Pituitary abscess**
  Pus with evidence of bacterial infection

- **Cranial irradiation**
  May be associated with cerebral vasculitis

- **Haemochromatosis**
  Often marked iron deposition in the pituitary

- **Infarction from apoplexy or Sheehan’s syndrome**
  Yields pathological features which change with the passage of time from the vascular catastrophe

The application of electron microscopy can sometimes help define pathology while cosecretion of more than one hormone by a single cell, suggested by immunostaining, can be confirmed by demonstration of specific mRNA products.

INVESTIGATION AND DIAGNOSIS

Investigation of hypothalamo-pituitary disorders involves the assessment of endocrine function – whether deficient, excessive or mixed – and delineation of the anatomy, size and topographical relations of any pituitary or parapituitary masses. Assessment of the effects of a mass conventionally focuses on the visual pathways. Quality of life (QOL) evaluation and psychometric testing are increasingly performed, especially in view of the long-term consequences of surgery or other therapeutic interventions (Fig. 15.8). Recognition of adult GH deficiency syndrome prompts serial assessment of bone density and body composition as well as cardiovascular risk factors such as lipid profile.

HORMONAL EVALUATION OF PITUITARY FUNCTION

Basal measurements adequately define most aspects of hormonal secretion, including pituitary–thyroid and –gonadal axes, PRL secretion and water metabolism (Fig. 15.9). The large variations in GH and ACTH/cortisol levels, which are determined by ultradian, circadian and stress-related mechanisms as well as classical negative feedback loops, often require dynamic testing (Fig. 15.10). Nevertheless a single 9 a.m. plasma cortisol measurement can provide adequate evidence of adrenal insufficiency if less than 180 nmol/L (6 µg/dl). Random GH measurements are useful only to exclude the diagnosis of acromegaly – this is unlikely if the value is less than 2 mU/L (1 ng/ml) – or for rough assessment of the degree of GH hypersecretion in known acromegaly since there is a strong correlation between the fasting GH measurement and the mean of serial samples taken over periods up to 24 hours, notwithstanding the frequently observed pulsatility of GH release in acromegaly. Measurement of IGF-I provides an integrated perspective of overall GH secretion. The level of IGF-I tends to be low in hypopituitarism even though it may lie within the age-related normal range in patients in whom stimulatory tests of GH reserve indicate
**Fig. 15.8  Psychometric consequences of pituitary disease and treatment by transsphenoidal/transfrontal surgery and radiotherapy***

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Transsphenoidal surgery</th>
<th>Transfrontal surgery</th>
<th>Medical treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>42.7</td>
<td>41.6</td>
<td>38.7</td>
<td>38.9</td>
</tr>
<tr>
<td>Years of education</td>
<td>10.9</td>
<td>11.3</td>
<td>11.5</td>
<td>11.6</td>
</tr>
<tr>
<td>Estimated duration of illness (years)</td>
<td>8.6</td>
<td>14.9</td>
<td>8.5</td>
<td>–</td>
</tr>
<tr>
<td>Estimated premorbid IQ</td>
<td>107.9</td>
<td>109.8</td>
<td>111.0</td>
<td>112.1</td>
</tr>
</tbody>
</table>

**Measures**

- Premorbid ability: National Adult Reading Test
- Attention: Digit subtest of Wechsler Adult Intelligence Scale (Revised)
- Memory: Auditory – verbal learning test
  - Story recall – from Wechsler Memory Scale
  - Recognition – memory test for faces
- Executive functions: Controlled oral word association test
  - Block design subtest of Wechsler Adult Intelligence Scale (Revised)
  - Trail-making test

**Results**

Three or more tests below tenth percentile

- Transsphenoidal = 30.4%, Transfrontal = 43.5%, Medical = 21.7%, Control = 4.3%

Radiotherapy had NO adverse effect on cognitive function


**Fig. 15.9  Basal blood tests for assessment of pituitary function**

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolytes (Na+/K+)</td>
<td>Total/free $T_4$ (and $T_3$)</td>
</tr>
<tr>
<td>Urea/creatinine</td>
<td>TSH</td>
</tr>
<tr>
<td>Osmolality</td>
<td>Prolactin</td>
</tr>
<tr>
<td>Calcium profile</td>
<td>FSH/LH</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>$\alpha$-subunit (if glycoprotein-producing tumour)</td>
</tr>
<tr>
<td>Fasting triglycerides</td>
<td>IGF-1</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Growth hormone (acromegaly)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>9am cortisol</td>
</tr>
<tr>
<td>LDL-C</td>
<td>ACTH (Cushing’s disease)</td>
</tr>
<tr>
<td></td>
<td>Midnight cortisol (Cushing’s disease)</td>
</tr>
<tr>
<td></td>
<td>Men: testosterone, SHBG</td>
</tr>
<tr>
<td></td>
<td>Women &lt; 50 years: $17\beta$ oestradiol</td>
</tr>
</tbody>
</table>
### Fig. 15.10 Dynamic tests of hypothalamo-pituitary-adrenal function

<table>
<thead>
<tr>
<th>Test</th>
<th>Contraindication</th>
<th>Precaution</th>
<th>Protocol</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin tolerance test (ITT)</td>
<td>Frank hypoadrenalism</td>
<td>Check 9 a.m. cortisol ≥ 180 nmol/L (6 µg/dl)</td>
<td>Fast patient overnight and weigh. Insert venous cannula. Obtain blood for plasma glucose and cortisol (and GH – see below) at 0, 30, 45, 60, 120 min. Inject 0.15 U soluble insulin/kg</td>
<td>Normal response: peak cortisol ≥ 550 nmol/L (18 µg/dl) if adequate hypoglycaemia achieved (≤ 2.2 mmol/L) (40 mg/dl) + appropriate symptoms. <strong>NB</strong> Only test validated clinically – ability to withstand surgical stress</td>
</tr>
<tr>
<td></td>
<td>Epilepsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac ischaemia including patients &gt; 70 years old – in whom IHD is likely</td>
<td>Check history and 12 lead ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagon test</td>
<td>Diabetes mellitus (30%) or vomiting (15%)</td>
<td>Prepare for nausea (30%) or vomiting (15%)</td>
<td>Fast patient overnight and weigh. Insert venous cannula. Obtain blood for plasma glucose, cortisol (and GH). Inject glucagon 1 mg i.m. (if weight &lt; 90 kg) 1.5 mg (if weight ≥ 90 kg). Repeat blood samples at 150 and 180 min after glucagon i.m. injection. <strong>NB</strong> Classical subcutaneous test: (same doses but samples at 0, 90, 120, 150, 180, 210 and 240 min)</td>
<td>Non-peak cortisol response ≥ 500 nmol/L (17 µg/dl) Post-glucagon subcutaneous injection peak time more variable, hence need for multiple samples</td>
</tr>
</tbody>
</table>
GH deficiency. Conversely levels tend to be raised in acromegaly, and this can be useful for monitoring the level of GH secretion following treatment. The level of IGF-binding protein 3 (IGF-BP3) is also related to mean level of GH secretion, but this measure is less sensitive though more specific than that of IGF-I.

Assessment of cortisol response to stress is essential in patients with pituitary disorders. Various tests are used.

**Assessment of GH reserve**

- **Insulin tolerance test (ITT)** This is the most powerful stimulus. Peak GH values usually exceed 20 mU/L (10 ng/ml). Lower values are found in old age. Adult onset GH deficiency is defined as ≤ 9 mU/L. (For details and precautions see Fig. 15.10)

- **Glucagon test** Peak values are as for ITT (see above)

- **Arginine test** This is used in some centres but responses do not correlate closely with ITT or glucagon in some patients (e.g. after irradiation)

- **Clonidine test** This is of minor value in children but ineffective, so useless, in adults

- **GHRH test** This directly tests pituitary reserve, bypassing vital hypothalamic mechanisms; hence it may give discordant and misleading results

- **Sex hormone priming** Peripubertal individuals should receive testosterone (boys) or ethinyl oestradiol (girls) prior to testing to establish maximum GH secretory capacity (see Ch. 16)
## Assessment of vasopressin secretion

Frank DI presents with thirst, polyuria including nocturia with the urinary volume exceeding 3 litres over 24 hours, and with a serum sodium level of more than 145 mmol/L. Milder degrees require evaluation with a water deprivation test including documenting response to desmopressin (DDAVP) (Fig. 15.11). On occasion, measuring plasma (arginine vasopressin, or AVP) responses to 5% saline infused at 0.04 ml/kg per minute for 2 hours will clarify issues (Fig. 15.12).

### Water deprivation test

<table>
<thead>
<tr>
<th>Time</th>
<th>Action</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>8am</td>
<td>Start water deprivation, empty bladder</td>
<td>Weigh1, Plasma osmolality1</td>
</tr>
<tr>
<td>9am</td>
<td>Urine1: volume1, urine osmolality1</td>
<td></td>
</tr>
<tr>
<td>10am</td>
<td>Urine2: volume2, urine osmolality2</td>
<td></td>
</tr>
<tr>
<td>11am</td>
<td>Urine3: volume3, urine osmolality3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repeat hourly until 3 successive urine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>osmolalities differ by &lt; 30 mosm/kg:</td>
<td></td>
</tr>
<tr>
<td>χ hour</td>
<td>Urineχ: volumeχ, urine osmolalityχ</td>
<td></td>
</tr>
<tr>
<td>χ+1 hour</td>
<td>Urineχ+1: volumeχ+1, urine osmolalityχ+1</td>
<td></td>
</tr>
<tr>
<td>χ+2 hour</td>
<td>Urineχ+2: volumeχ+2, urine osmolalityχ+2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inject desmopressin 2 µg im</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Finish test: allow water and food</td>
<td></td>
</tr>
</tbody>
</table>

N.B. This modification minimizes test time till patient’s maximum urinary concentration is achieved:
- distinguishes partial from complete DI
- distinguishes cranial from nephrogenic DI

### Imaging of the hypothalamo-pituitary region

MRI is the modality of choice in most cases. However, the presence of ferromagnetic material (e.g. some ocular prostheses) is an absolute contraindication. MRI is safe but may prove claustrophobic, noisy and prolonged for some patients. Enhancement with gadolinium very rarely causes adverse reactions. Pituitary adenomas as small as 3 mm can be detected (Fig. 15.13). T1 and T2 signal characteristics inform about tumour qualities such as water content, haemorrhage and fibrosis. The optic chiasm is visualized well and its relationships to the pituitary well defined (Fig. 15.14). The posterior lobe normally appears as a
hyperintense signal (Fig. 15.15). The lateral relations of the pituitary show up well and give
evidence of abutment upon or invasion of cavernous sinuses (Fig. 15.16).

CT scanning is still useful – especially when access to MRI is limited or delayed. Pituitary
tumours are almost as well imaged but chiasmal and cavernosal relations are less so. Bony
relations including erosion are particularly well delineated (Fig. 15.17). The irradiation load
is high so efforts are made to avoid the eye lenses; this may involve the uncomfortable
‘hanging head’ position to obtain coronal images. Dental fillings may cause streak artefacts.
Contrast media give useful information but may be associated with severe reactions.
Calcified lesions such as craniopharyngiomas are well demonstrated, but MRI may also be required to show the full extent of tumour (Fig. 15.18).

Angiography may be needed to display arterial anatomy – for instance if aneurysms are suspected (Fig. 15.19). Ectatic loops of carotid arteries are often seen in acromegaly. Magnetic resonance angiography (MR-A) is of use, though has a lower exclusion value for small aneurysms than conventional angiography.
Fig. 15.16  MRI illustrating a pituitary tumour invading the cavernous sinus (enwrapping the intracavernosal carotid artery), (a) before and (b) after gadolinium.

Fig. 15.17  CT scan demonstrating bony erosion by a pituitary tumour.

Fig. 15.18  (a) and (b) MRI versus (c) and (d) CT scanning of craniopharyngioma.
INVESTIGATION OF ACROMEGALY

A number of tests may be appropriate:

- **Random GH**
  - Values less than 2 mU/L (1ng/dl) exclude acromegaly

- **IGF-I**
  - Above the age-matched normal is suggestive – investigate further

- **Oral GTT with GH measurements**
  - The normal response is a fall to less than 2 mU/L (1ng/dl) (Fig. 15.20)

- **MRI**
  - Add, if necessary, MR-A or angiogram, and skull X-rays (Fig. 15.21)

- **PRL**

- **Thyroid function tests**
  - Plus a thyroid scan if goitre is present

- **Gonadotrophins and sex steroid measurements**
  - As clinically indicated

- **ECG, chest X-ray**
  - Plus echocardiogram if there is hypertension

- **Serum calcium, phosphate, 24 hour urinary calcium**
  - Plus if necessary X-ray of the renal tract

- **Full blood count**
  - If there is anaemia, bowel symptoms, or a family history of colon cancer add colonoscopy

- **Dorsolumbar spine X-ray, DEXA (dual-energy X-ray absorptiometry)**
  - If there is backache, kyphosis, or loss of height

- **Nerve conduction studies**
  - If there is neuropathy, especially carpal tunnel syndrome

- **Sleep studies**
  - If there is snoring or daytime somnolence

- **Skin thickness measurement**
  - (Fig. 15.22)

- **Ring size measurement**
  - (Fig. 15.23)

INVESTIGATION OF CUSHING’S DISEASE

In patients with established Cushing’s syndrome (see Ch. 18) the following tests should be performed:

- **Low dose dexamethasone test**
Acromegaly
(paradoxical rise post-glucose)

Acromegaly
(inadequate suppression post-glucose)

Fig. 15.20  GTT showing GH responses in a patient with acromegaly and in a normal individual.

Fig. 15.21  Skull X-ray of a patient with acromegaly showing an enlarged sella, thickened calvarium, large frontal air sinuses, occipital bossing and prognathism.

Fig. 15.22  Skinfold measurements in acromegaly.
CRH test
Desmopressin test
MRI scan
Inferior petrosal sinus sampling

Petrosal sinus sampling is useful for differentiating pituitary from ectopic sources of ACTH secretion in Cushing’s syndrome. Catheters are introduced via the femoral veins and passed under radiological screening up through the heart and jugular veins to the inferior petrosal sinus (IPS). Conventionally, a catheter is inserted each side and a further line established for peripheral venous sampling. After central (right and left) and peripheral blood samples are taken, CRH 100 mg is injected intravenously. Repeat blood samples are taken from both IPSs and the peripheral vein three times over a 15 minute period following the CRH injection for ACTH measurement (in EDTA tubes, sent to the laboratory on ice, rapidly spun and frozen; ensure accurate labelling). Rare but serious complications, including haematoma, thrombosis and brainstem lesions, have led to the development of sequential sampling of each IPS after CRH injection (since the ACTH elevation from pituitary lesions is prolonged), as this has lower morbidity (Fig. 15.24). If ACTH values from either IPS exceed twice the simultaneous peripheral value a pituitary source is strongly suggested. Note though that the IPS side with peak ACTH values is not necessarily the side of the pituitary tumour.

CLINICAL FEATURES

PITUITARY TUMOURS

**Space-occupying features**

- Headache
- Visual disturbance
- Hypopituitarism
- Hydrocephalus, hypothalamic syndrome
- Cerebrospinal fluid (CSF) leak
- Epilepsy

Headache, which is common with pituitary tumours even of modest size, is often attributed to pressure on the dura mater, especially the diaphragma sellae. However, rarely it is due to massive tumours causing raised intracranial pressure.

Pituitary infarction is commonly partial and may be asymptomatic but major episodes cause pituitary apoplexy characterized by the following features:
Features of pituitary apoplexy

- Sudden, severe headache
- Meningism (with evidence of subarachnoid haemorrhage)
- Cavernous sinus involvement – diplopia, ophthalmoplegia, ptosis and facial pain
- Acute anterior pituitary failure – complete or partial including isolated ACTH or TSH deficiency (see Ch. 14)
The most common visual disturbance is chiasmal compression. Classically this begins with upper outer field loss progressing to bitemporal hemianopia or even complete blindness. Clinical testing by confrontation should begin with a red pin (Fig. 15.25) as loss of colour vision frequently long predates the inability to see finger movements. Other visual tests include the use of Ishihara colour charts and evidence of relative afferent pupillary defect (Fig. 15.26). Assessment of visual acuity should involve the reading of lines of print, as often letters become lost at the beginning and end of lines. Pituitary tumours may be asymmetrical with striking differences in field defects between the right and left eyes. Fundoscopy often reveals optic atrophy with established chiasmal compression (Fig. 15.27); papilloedema is rare. Ophthalmoplegia indicates cavernous sinus involvement.

Hypopituitarism due to pituitary tumour characteristically progresses sequentially:

- **GH deficiency.** Is the first detectable feature
- **Gonadotrophin deficiency.** Appears early on, with LH deficiency preceding that of FSH
- **PRL excess.** Is often early but modest; it is due to stalk compression
- **ACTH deficiency.** Is a late feature
- **TSH deficiency.** Is usually last to develop
- **DI.** If present at presentation this strongly suggests a parapituitary disorder

**GROWTH HORMONE DEFICIENCY**

GH deficiency in childhood is dealt with in Chapter 16. Adult GH deficiency is diagnostically valuable and clinically important (Fig. 15.28), since recombinant GH therapy is available. Gonadotrophin deficiency in premenopausal women is generally recognized early on account of primary or secondary amenorrhoea, infertility or loss of libido. Men often delay presentation on developing impotence or loss of libido, though with wider recognition of effective management of erectile dysfunction this pattern is reversing, provided other practitioners check for hormonal causes. Gonadal dysfunction is augmented...
by hyperprolactinaemia – this is principally due to reduction in the frequency of GnRH release. Galactorrhoea is not common or correlated with level of PRL excess and is rare in men.

**HYPERPROLACTINAEMIA**

Hyperprolactinaemia may be caused by any of the following:
- Prolactinoma
- Functionless pituitary adenoma (a stalk effect)
Hypothalamic disease due to tumour, granuloma, or irradiation

Primary hypothyroidism

Dopamine antagonists such as phenothiazines, butyrophenones, metoclopramide and domperidone

Opioid peptides and alkaloids

Oestrogen – in high dosage, or pregnancy

H₂ antagonists – such as intravenous (not oral) cimetidine

Polycystic ovary syndrome (PCOS)

Acromegaly

McCune–Albright syndrome (Fig. 15.29)

Chronic renal failure

Hepatic cirrhosis

Chest wall disease

Microprolactinomas (less than 10 mm maximum diameter) are common and do not cause space-occupying problems, with the occasional exception of headache; nor are they usually associated with other hormone deficiencies, with the exception of the expected hypogonadism and less often GH deficiency. Macroadenomas secreting PRL contrast with large functionless tumours causing hyperprolactinaemia by stalk compression that interferes with delivery of hypothalamic dopamine, thus disinhibiting normal pituitary lactotrophs. Clinical distinction between the two tumours usually depends on the level of PRL secretion: values over 8000 mU/L (400 ng/ml) strongly suggest macroprolactinoma, whereas those less

---

**Adult onset GH deficiency**

<table>
<thead>
<tr>
<th>Body composition</th>
</tr>
</thead>
<tbody>
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| Mortality increased? cause? cardiovascular? |

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**Fig. 15.28** Features of adult onset GH deficiency.
than 2000 mU/L (100 ng/ml) suggest a stalk effect. Macroprolactinomas may shrink markedly with dopamine agonist therapy (see below).

Hypothalamic lesions such as craniopharyngiomas, or those caused by surgical damage or irradiation, may cause modest hyperprolactinaemia by diminishing dopaminergic tone.

HYPOPITUITARISM
ACTH deficiency may present either chronically or acutely, precipitated by intercurrent illness.

**Clinical features**

**Chronic:**
- Fatigue
- Disproportionate pallor of skin compared with the mucous membranes (i.e. not due to anaemia)
- Orthostatic hypotension
- Hyponatraemia
- Low grade pyrexia of unknown origin (sepsis excluded)

**Acute:**
- Haemodynamic collapse
- Nausea and vomiting
- Obtunded consciousness associated with severe hyponatraemia
- Prerenal uraemia (less commonly than in primary adrenal failure)
- Hypoglycaemia
TSH deficiency presents with the usual features of hypothyroidism but is often milder than primary hypothyroidism. Myxoedema is not usually seen in secondary hypothyroidism although the skin is often dramatically cold and dry to the touch.

TUMOURS WITH EXTRASELLAR EXTENSION
Large tumours can extend upward compressing the hypothalamus and third ventricle. Hydrocephalus may result in dementia, loss of balance and abnormalities of micturition. Invasion of the temporal lobes can cause epilepsy. Many neural problems develop, often years later, after surgery or radiotherapy. Tumours eroding through the pituitary fossa and sphenoid bone can lead to the subarachnoid space communicating with the nasopharynx, resulting in CSF rhinorrhoea and the potential for meningitis.

HYPERSECRETING PITUITARY TUMOURS
Cushing’s disease – see Ch. 18.

ACROMEGALY
GH excess causing gigantism (Fig. 15.30) prepubertally occurs rarely. Apart from the increased growth of long bones leading to an ultimate height often in excess of 2 metres, this is associated with kyphoscoliosis and distortions of the rib cage. The pituitary tumours are frequently large.

Adult onset acromegaly is most frequently diagnosed in patients in the middle years of life, but retrospective analysis of photographs often discloses developing features becoming apparent 10 or more years before diagnosis (Fig. 15.31).

Clinical features

- Enlargement of hands (becoming fleshy, so rings need enlarging) (Fig. 15.32) and of feet (becoming broader)
- Thick skin with deep creases, increased sweating and sebum production (Fig. 15.33)
- Hypertension, left ventricular hypertrophy and congestive cardiac failure
- Soft tissue enlargement – such as in the nose, tongue (Fig. 15.34), larynx, or viscera
- Prognathism and increased interdental spacing (Fig. 15.35)
- Visual field defects
- Obstructive sleep apnoea
- Goitre, which is multinodular, and sometimes toxic
- Hyperprolactinaemia, hypogonadism and galactorrhoea
- Osteoporosis
- Osteoarthritis
- Colonic polyps and carcinoma
- Impaired glucose tolerance and diabetes mellitus
- Carpal tunnel syndrome
- Hirsutism (Fig. 15.36)
- Hypopituitarism
- Myopathy
GONADOTROPHINOMAS
These have only relatively recently been recognized as a distinct entity. Some claim they constitute the majority of ‘functionless’ pituitary tumours as judged by immunostaining and
secretion in cell culture after removal at surgery. However, the serum gonadotrophin levels are normal and in addition this claim does not account for the well-recognized inclusion of normal pituitary tissue in many pituitary tumours. Even raised gonadotrophin levels cannot help diagnosis in postmenopausal women – hence the readier recognition of tumours hypersecreting gonadotrophins in men. They usually dominantly secrete FSH with or without excess glycoprotein α-subunit production, LH, LHβ or indeed any other combination. They have been characterized as benign tumours with low rates of dural invasion which eventually present having grown large and causing primarily visual symptoms as well as hypopituitarism. Against this concept of indolent growth is the capacity of documented gonadotrophinomas to recur rapidly postoperatively accompanied by deteriorating vision, which is only partially abrogated by radiotherapy. Men with these tumours often have extremely large testicles caused by an increase in seminiferous tubules.

**TSH-OMAS**

These are rare, causing thyrotoxicosis with goitre but no eye signs of Graves’ disease. Levels of T4 and T3 are raised, accompanied by normal or raised TSH levels and often excess glycoprotein α-subunit production. Less frequently TSH-omas also secrete PRL, GH or
gonadotrophins. They are frequently large at presentation with effects due to mass, as well as thyrotoxic features. They need to be distinguished from thyroid hormone resistance, which is usually due to mutations in exons 9 and 10 of the thyroid hormone β-receptor, and in which there is no excessive α-subunit production and no association with pituitary tumours (see Ch. 17).
OTHER PARASELLAR AND SUPRAPITUITARY LESIONS

Craniopharyngiomas
These are the commonest tumours affecting the hypothalamo-pituitary region in childhood. They may, however, present at any age.

Clinical features

- **Infancy.** Features of raised intracranial pressure and gross visual impairment
- **Childhood.** Raised pressure and short stature
- **Puberty.** Endocrine insufficiency causing delayed or arrested puberty, poor growth and DI
- **Middle/old age.** Headache, visual defects, usually also hypopituitarism

They are tumours arising from Rathke’s pouch (Fig. 15.37) and are frequently cystic and solid (Fig. 15.38). Cysts contain cellular debris, cholesterol crystals and dark oily liquid, and β-hCG is usually detectable. They are capable of widespread extension reaching the frontal region, temporal fossae and brainstem. The solid elements frequently calcify; they are more conspicuous in childhood, but probably increase with time. Malignant transformation is exceedingly rare but the extensive spread from the hypothalamus to other critical central nervous sites means they often behave in a highly damaging fashion.

Fig. 15.36  **Hirsuties in a woman with acromegaly.**
Germinomas are the commonest germ cell tumours of CNS and closely resemble gonadal tumours. They usually present in young teenage girls with headache, visual loss, anterior pituitary failure especially affecting growth and diabetes insipidus, which should alert the clinician that this is not a routine pituitary tumour. Boys tend to have pineal tumours, often also with suprasellar components. Secretion of β-HCG and α-fetoprotein into blood and CSF may occur in germ cell tumours and seeding can occur down the neuraxis.

Other lesions such as optic nerve glioma and sphenoid ridge meningioma cause primarily visual disturbances, but astrocytomas and other tumours can cause hypothalamic dysfunction. Pituitary damage can follow trauma, especially in abused infants who can develop varying
degrees of damage including panhypopituitarism, which is often apparent only years later when there is growth failure. Note that psychosocial deprivation can also cause GH deficiency but this often reverses rapidly on hospitalization or on being taken into care. Road traffic accidents can cause pituitary stalk section, which classically causes DI but also anterior pituitary failure. Other consequences include cortical blindness, and emotional and cognitive difficulties.

VASCULAR DISORDERS OF THE PITUITARY
Any of the following factors may lead to pituitary infarction:
- Pregnancy
- Diabetes mellitus
- Anticoagulation
- Pituitary tumours
- Cerebral aneurysms
- Coronary artery bypass grafting
- Old age

Pituitary failure can occur after vascular catastrophes such as infarction or haemorrhage. Sheehan’s syndrome may follow massive ante- or postpartum haemorrhages with hypotensive shock; prompt blood transfusion should prevent this, however. Hyperplasia and hypertrophy of lactotrophs in pregnancy render the pituitary blood supply vulnerable. Clinical symptoms occur only when more than 90% of the pituitary volume has been destroyed.

Clinical features
- Failure of lactation (hypoprolactinaemia)
- Other features of anterior pituitary failure (e.g. amenorrhoea)
- ACTH and TSH deficiency, which may declare only much later with patients classically becoming torpid, bedbound and losing all interest and initiative

Diabetes mellitus is said to enhance the risk of pituitary infarction but the incidence is very small, and this also applies to anticoagulation. Histological examination of pituitary tumours frequently reveals areas of infarction or haemorrhage of varying age that are usually symptomatically and hormonally insignificant.

Pituitary apoplexy (see p.194) may prove lethal as a result of subarachnoid haemorrhage or of easily overlooked adrenal insufficiency if the condition is not recognized. Morbidity includes ophthalmoplegia as well as pituitary deficiency – which may include complete extirpation of a hypersecreting tumour such as acromegaly. When partial deficiencies arise they do so unpredictably with, for example, ACTH or PRL deficiency but preservation of gonadotrophin secretion. This feature is typical of vascular insults causing selective losses of pituitary hormones and contrasts with the progressive pattern of growing pituitary adenomas.

Ectatic loops of carotid may occupy and expand the pituitary fossa with consequent endocrine deficiency but their recognition is much more important if surgery is planned. Coronary artery bypass grafting involves non-pulsatile flow with anticoagulated blood,
which has been documented to produce major disturbances in pituitary hormone secretion and occasional early cases of pituitary apoplexy. Delayed presentation also occurs with loss of libido, secondary hypothyroidism and adrenal insufficiency, which is often indicated by persistent hyponatraemia. Imaging of the pituitary shows marked loss of volume. The same pattern can occur idiopathically in old age when the presenting feature is often orthostatic hypotension.

**DEFICIENCY SYNDROMES**

Any of the following hypothalamic releasing factors may be lost:

- GnRH (with anosmia: Kallman’s syndrome)
- GHRH
- ACTH
- Thyrotropin-releasing hormone (TRH)
- Dopamine
- Somatostatin
- Multiple deficiencies

Deficiency of GnRH may be inherited as an isolated defect, or be due to a mutation in an adhesion molecule that leads to failure of migration of GnRH neurons from their origin in the olfactory placode to the median eminence. If there is associated anosmia it is termed Kallman’s syndrome, and may also include other midline defects such as cleft lip and palate and renal tract anomalies (Fig. 15.39). Acquired GnRH deficiency accompanies severe weight loss especially anorexia nervosa and stress; it may be mediated by endogenous opioids and may follow excessive physical activity (usually also causing loss of body fat).

Isolated GH deficiency is rarely total, and is more often due to congenital GHRH deficiency – hence sufferers respond to exogenous GHRH, which limits its use in diagnosing GH deficiency but permits its use as a therapy (see Ch. 16). Isolated ACTH deficiency is usually acquired (presenting variously with hypoglycaemia, weight loss, hypotension and other features of cortisol deficiency). Alcohol abuse may be a factor. Most cases appear to be due to primary pituitary ACTH deficiency but there are also well-recorded cases that are apparently due to CRH deficiency. TRH deficiency is rare but may occur as an isolated acquired phenomenon. Dopamine deficiency is postulated as underlying ‘idiopathic hyperprolactinaemia’ but the possibility of prolactinomas too small to be visualized cannot be discounted. Somatostatin deficiency rarely presents since most pathological processes simultaneously affect GHRH. However, Alzheimer’s disease is notably associated with deficiency of somatostatin amongst other neurotransmitters. Such patients often have modestly elevated GH levels though this may reflect IGF-I deficiency occasioned by their frequent though ill-explained cachexia.

Multiple hypothalamic hormone deficiencies can occur congenitally or after trauma. A common cause is cranial irradiation, which causes dose- and time-dependent GH and gonadotrophin deficiencies that are secondary to releasing factor loss, and hyperprolactinaemia due to dopamine deficiency. Hypothalamo-pituitary—adrenal and –thyroid axes may also become deficient, but usually much later after radiotherapy, which points to the need for continuing surveillance and repeated retesting over the years.
PITUITARY ABSCESS
Pituitary abscess may arise following injury causing fracture to the base of the skull, which allows infectious agents to enter the pituitary from the nasopharynx.

Clinical features

- Moderate hyperprolactinaemia
- Diabetes insipidus
- Expanding pituitary lesion, thick-walled, lytic centre, thick pituitary stalk

Awareness of this syndrome allows transsphenoidal surgery with appropriate antibiotic cover.
OTHER CONDITIONS

Granulomatous conditions
Granulomatous conditions such as neurosarcoid and syphilis can affect the pituitary or hypothalamus. Tuberculous meningitis causes a chronic basal meningitis that often calcifies and is associated with profound pituitary failure. Idiopathic granulomatous hypophysitis has also been described.

Lymphocytic hypophysitis
Lymphocytic hypophysitis is most commonly associated with the third trimester of pregnancy or the puerperium, in association with a pituitary mass and often initially ACTH and TSH deficiency. Diabetes insipidus is sometimes also seen. In such patients it may resolve spontaneously, whereas in older women and in the few men in whom it has been recorded the disease seems more permanent and profound. Concomitant Hashimoto’s disease and pernicious anaemia occurring together with limited pathological material demonstrating lymphocytic infiltration suggests an autoimmune aetiology.

Langerhans cell histiocytosis
This condition is associated with the following triad of clinical features:

- Punched-out skull lesions (Fig. 15.40)
- Exophthalmos
- DI

Anterior pituitary deficiency also occurs, especially GH deficiency. Some patients develop presenile dementia.

Fig. 15.40  Skull X-ray showing punched-out lesions due to Langerhans cell histiocytosis.

Fig. 15.41  Cutaneous lesions of xanthoma disseminatum.
Xanthoma disseminatum
This rare condition may present with cutaneous (Fig. 15.41) and mucosal xanthomatous lesions, anterior and posterior pituitary failure, deposits within the skull causing epilepsy and tracheal stenosis requiring tracheotomy.

Wegener’s granulomatosis
This condition, characteristically affecting the respiratory and renal tracts, may cause pituitary involvement with mass effects and endocrine deficiency.

Metastatic disease
Metastatic disease to the hypothalamus is especially common in carcinoma of the breast and bronchus. If there is concomitant DI then this usually presages an early demise. Autopsy studies frequently reveal pituitary metastases with no clinical symptoms. However, occasionally apparently solitary metastases in the pituitary cause chiasmal compression, for instance in renal carcinoma (Fig. 15.42).

Iron overload
Conditions associated with iron overload (see Ch. 19) such as haemochromatosis and β-thalassaemia following multiple transfusions characteristically deposit iron in gonadotrophs causing primary pituitary gonadotrophin deficiency.

MANAGEMENT

HYPOPITUITARISM
Ideally each deficient hormone, or more frequently target organ hormones, should be replaced in as physiological a manner as possible. This is largely limited by practical considerations, however.

Adrenal insufficiency
Adrenal insufficiency, which is usually defined as an inability to respond with adequate cortisol secretion to stress, is usually treated by replacement doses of glucocorticoid. The physiological steroid hydrocortisone is preferred because its concentration can be checked by serial measurements. Conventionally, two-thirds of the total is given in the early morning to achieve a peak level approximating the time of maximum circadian secretion in normal individuals, and the remainder is given at 4–6 p.m. (because administration late at night can disturb sleep and cause polyuria). The usual regimen of 20 mg and 10 mg respectively is now
considered excessive for many people, and carries the risk of osteoporosis and other side-effects. Some patients prefer a thrice-daily pattern, in which two small doses at lunch and tea follow the major morning dose. Prednisolone 2.5 mg twice daily, or 5 mg and 2.5 mg, may be preferred especially if given in an enteric-coated form; in the US this is also significantly cheaper than hydrocortisone. Patients on anticonvulsants may clear steroids more quickly so may need higher and more frequent doses.

Secondary hypothyroidism is easily dealt with using levo thyroxine, building up over weeks to a final dose of 75–200 µg daily. Obviously TSH cannot be used to monitor therapy: this should be done clinically while aiming for thyroxine levels to be in the upper normal range. Measurement of T₃ levels may be helpful. Thyroxine should not be given to ACTH-deficient patients until they have been on replacement glucocorticoid for 48 hours; this avoids the theoretical risk of precipitating an adrenal crisis.

Hypogonadism
Male patients with hypogonadism require testosterone to maintain libido, sexual function and secondary sexual characteristics, but also for general vigour, maintenance of muscle bulk and strength and prevention of osteoporosis. Oral testosterone undecanoate or sublingual testosterone preparations are rarely adequate. The main route is intramuscular, using testosterone esters usually administered every 2 weeks (the classical monthly treatment often leaves the patient with subnormal levels for 2 weeks). There has been a revival of testosterone pellet implant treatment, in which a dose of 600 mg is delivered subcutaneously every 4–6 months. Recently transdermal patches have been introduced, which were originally applied to shaved scrotal skin, but more recently to body skin. In women less than 50 years of age, hormone replacement therapy (HRT) is required, or a low dose oral contraceptive pill up to the age of 35 in cases where infertility cannot be assumed.
Growth hormone deficiency
GH is now widely available as a synthetic recombinant DNA product but this is very expensive and requires subcutaneous administration. In selected adult patients GH therapy can improve a number of the clinical features:

Clinical features
- Truncal obesity
- Lack of skeletal muscle and physical strength
- Exercise capacity
- Adverse lipid profile
- Lack of vitality
- Osteoporosis
- Reduced total body water

The dose per unit weight is much less than that required to optimize growth in children. Daily nocturnal subcutaneous injections are recommended but thrice-weekly injection is effective. Very small doses are used initially to avoid rapid overcorrection of body water, which causes joint pains and carpal tunnel syndrome. Women tend to need higher doses. A 6 month trial using physical and QOL assessment is recommended. If no clear-cut objective or subjective improvement is shown after this period then treatment should be stopped. Serum IGF-I should be monitored and GH dosage adjusted to keep it within the age-related normal range.

If there is osteoporosis, GH is given in combination with sex steroids and optimal hydrocortisone and thyroxine dosage.

DIABETES INSIPIDUS
Frank DI requires desmopressin, which is usually administered by a metered intranasal spray that provides 10 \( \mu \text{g} \) per squirt. A dose of 10–20 \( \mu \text{g} \) is administered at bedtime but a second dose may be needed in the morning. Overdosage leading to water intoxication must be avoided. This is particularly difficult in patients with hypothalamic damage to the thirst centre in addition to DI. They require a strict regimen of fluid input, adjusted appropriately in hot weather and monitored by weighing at the same time daily, or twice daily in the event of problems. Regular biochemical checks are needed and should be repeated when clinically required. Milder degrees of DI can be managed by oral DDAVP, which is especially useful in children or patients with cognitive and visual problems. In some patients medication with carbamazepine will suffice.

Postoperative DI may require intramuscular DDAVP for some days, especially following transsphenoidal surgery when nasal packs are in place. Postoperative DI is often temporary, lasting only days or weeks. Occasionally a triphasic response occurs (Fig. 15.43). It is advisable for patients on DDAVP after surgery to try without it every few months at a time when sudden return of polyuria will not prove inconvenient. If replacement is still needed they will experience unequivocal symptoms within 24 hours of discontinuing DDAVP.

Some patients with hypothalamic disease, rather than DI, have disturbed thirst and develop primary polydipsia. This must not be mistaken for DI as antiuretic treatment causes water intoxication. This has been particularly recorded in neurosarcoid conditions.
OTHER CAUSES OF POLYURIA

Profound polyuria after surgery for aneurysm of the anterior communicating artery, and infrequently for other intracranial conditions, may be due to cerebral salt wasting. This should not be mistaken for DI and treated with DDAVP. In fact it causes greater loss of salt than water, hence there is marked hyponatraemia, so there is no justification for confusion. Indeed it is frequently mistaken for the syndrome of inappropriate ADH secretion (SIADH) and treated by fluid restriction. However, the polyuria makes this diagnosis untenable and such management dangerous. The appropriate treatment is infusion of normal saline in quantities matching the previous, carefully measured, 24 hour urinary sodium losses. This must be continued for as long as the condition requires, and chronic cases may require oral sodium chloride supplementation. There have been suggestions that the underlying defect is excessive secretion of brain antinatriuretic peptide; if these are substantiated this may lead to the development of antagonist drugs.

Other causes of polyuria such as diabetes mellitus may occur and require appropriate treatment. Hypercalciuria is common in acromegaly, especially if there is associated hypercalcaemia from another cause; the most common of which is hyperparathyroidism due to MEN-1. Hypercalcaemia should be treated appropriately (see Ch. 14). Hypercalciuria may respond to low dose thiazide. This is also helpful in nephrogenic DI, in which, if necessary, amiloride and a prostaglandin synthetase inhibitor such as indomethacin should be added.

PITUITARY TUMOURS

Small functionless tumours causing neither mass effects nor endocrine dysfunction may be incidentally discovered during CT or MRI scans performed for other reasons. Having documented their innocuous nature no action is needed, but repeat MRI scans are recommended every 2 to 5 years unless clinical features appear.

Functionless tumours causing visual disturbance or other mass effects require surgical removal with few exceptions. The transsphenoidal approach is preferred where possible, including in those tumours with extensive suprasellar extension, when the roof of the
resected tumour will be seen to descend. In contrast, tumours with eccentric lobulated extensions and most parasellar lesions are approached transcranially. However, the classical approach involving a retraction of the right frontal lobe frequently gives rise to infarction and cerebromalacia as well as serious psychological disabilities. Depending on the completeness of resection and whether there is any evidence of dural invasion (which is clinically difficult to assess) many patients require external radiotherapy, which is a skilled technique.

**External radiotherapy**

A suggested regimen is:

- **Maximum tumour dose**: 4500 cGy
- **Maximum daily dose**: 180 cGy
- **Number of fractions**: 25, over 5 weeks
- **Use of three ports**: Rotating through each in turn (*Fig. 15.44*)
- **Individual clear Perspex mask**: Moulded for each patient (*Fig. 15.45*)

Radiotherapy reduces the recurrence rate strikingly. Possible long-term side effects include second tumours in the field of irradiation (gliomas often responding poorly to treatment), progressive hypopituitarism, and vasculitis particularly affecting the visual pathways. Conventional radiotherapy cannot be repeated. If tumours recur then further surgery may be
required. Newer techniques under evaluation include $\gamma$-knife stereotactic radiotherapy and photodynamic therapy.

Visual field defects improve in most patients, often completely, though in an appreciable minority they are unchanged and very rarely may worsen postoperatively. Severe headache tends to improve significantly following surgery. Pituitary function may improve after the removal of small to moderate tumours (microadenomas $\leq 10$ mm maximum diameter) but with large macroadenomas there is usually no change or significant worsening of function. This implies full endocrine testing preoperatively.

A few centres recommend no steroid cover in patients with normal ACTH reserve but most suggest the following regimen:

- Hydrocortisone 100 mg i.v. with premedication
- Hydrocortisone 100 mg i.v. 8 hourly for 24–48 hours
- Hydrocortisone 50 mg i.v. 8 hourly for a further 24–48 hours
- Hydrocortisone by mouth rapidly reducing to 15 mg on waking, 5 mg at 6 p.m.

Patients should be discharged on the last dose with appropriate advice (see above).

Approximately 6 weeks after surgery stop hydrocortisone for 24 hours and check levels of ACTH and GH reserves using the ITT or glucagon stimulation test; also recheck electrolytes, PRL, and thyroid and gonadal status. If there are adequate ACTH reserves then stop hydrocortisone immediately (with no tailing of doses). If the reserves are borderline then consider stopping but advise the patient to have a standby supply to cover times of stress. Whenever possible reduce the daily hydrocortisone to 20 mg daily (see above regimen). Make adjustments to cover replacement requirements, and consider the need for GH therapy (see above). Patients will require follow-up scans, beginning within a year of surgery and 2–5 yearly thereafter. Endocrine surveillance, especially after radiotherapy, should continue indefinitely.

ACROMEGALY

The first-line treatment for most patients is transsphenoidal surgery. Cure rates with small tumours approximate 80% but reduce markedly with increasing size. The aim should be a normal IGF-I and a mean GH level over 24 hours of less than 5 mU/L (2.5 ng/ml).
Medical treatment of acromegaly may suffice alone in mild cases, especially in elderly patients as in these the disease appears more indolent than in the young. As the sole treatment or as an adjuvant to surgery, radiotherapy, or both, if there is an adequate response to bromocriptine then try up to 30 mg daily or cabergoline 0.25–1 mg once to thrice weekly. If the octreotide response is adequate then use 50–100 µg subcutaneously one to three times daily. Octreotide often causes transient abdominal pain or diarrhoea for a week or so. Gall stones may develop but are seldom clinically troublesome. Watch for diabetes mellitus developing or worsening. Headache may disappear within minutes of octreotide injection. Lanreotide (another somatostatin analogue) and octreotide depot preparations are now available, which act for 7–14 days and 28 days plus respectively. Currently under trial is the use of the synthetic GH antagonist Pegvisomont, which may reduce IGF-I and improve clinical features in patients with resistant acromegaly.

PROLACTINOMA
Dopamine agonist therapy (bromocriptine, quinagolide or cabergoline) reduces PRL levels in almost all cases, often back to normal. Drugs are usually regarded as first-line therapy for most patients with micro- or macroprolactinomas for a number of reasons:
● Reversal of amenorrhoea usually occurs within months and in 90% after a year’s treatment
● Fertility responds rapidly and almost as satisfactorily
● Galactorrhoea usually diminishes or disappears
● Tumours usually shrink often strikingly with improvement in visual fields
● Drugs are usually withdrawn in pregnancy but bromocriptine is safe to continue
● Pregnancy-associated tumour expansion can be rapidly reversed
● Impotence in men is usually corrected if testosterone is normalized
● Cessation of therapy allows tumour re-expansion especially after short-term treatment

Surgery may be considered in the following circumstances:
● Rapid visual deterioration
● Resistance to drugs (rare), resulting in inadequate PRL fall or tumour shrinkage
● Intolerable side-effects, such as nausea, dizziness, headache, or white hands
● A patient preference
However, surgery rarely cures macroprolactinomas and often involves hypopituitarism. The benefits of radiotherapy are delayed but may constrain tumour expansion in pregnancy.

**CUSHING’S DISEASE**

When a secure diagnosis has been achieved (itself a major challenge), most patients are submitted to pituitary surgery. This is a highly specialized area, however, and so surgery should be confined to the few neurosurgeons with sufficient experience and expertise.

Tumours are usually small – often only a few millimetres in diameter – and may not show up on MRI or CT scanning. At transsphenoidal surgery, serial sagittal cuts through the pituitary may be needed to disclose the tumour. Sometimes nothing is found and then near-total hypophysectomy may be required. Pathological examination may not demonstrate a tumour, simply hyperplasia or indeed no obvious abnormality, even when clinical and biochemical evaluation postoperatively indicates a cure. The finding of undetectable morning cortisol within days of surgery (before the first dose of hydrocortisone) indicates a likely cure though late relapses are well recognized. Low-normal cortisol levels are associated with higher and earlier relapse rates but can be followed by long-term remissions. A clear failure to improve biochemistry can indicate the need for early further surgery. There is some dispute over whether preoperative reduction in hypercortisolaemia by adrenal-blocking drugs such as metyrapone and ketoconazole improves the perioperative course (see Ch. 18).

Bilateral adrenalectomy as primary therapy for Cushing’s disease has largely been abandoned because of the risk of causing Nelson’s syndrome (Fig. 15.46). Most ‘cured’ patients require corticosteroid replacement therapy for at least a year after pituitary surgery, and sometimes permanently. Radiotherapy has a role but is less often used than formerly. Rare macroadenomas are especially difficult to treat and may exceptionally metastasize.

![Fig. 15.46  (a, b) Nelson’s syndrome in a patient treated for Cushing’s disease by bilateral adrenalectomy.](image-url)
CRANIOPHARYNGIOMAS
These require surgery for mass effects and almost invariably require anterior and posterior pituitary replacement therapy, especially after surgery. Though radical surgery is optimal for prevention of recurrence, incomplete resection is often all that can be safely achieved without damaging critical neural centres, depending on the extent of the tumour. Radiotherapy is often combined with surgery – which is usually transcranial and carries quite a high morbidity. The radiotherapy dose is generally slightly higher than with pituitary tumours but daily fractions are restricted to 180 cGy. Other problems are common including hydrocephalus requiring ventriculo-peritoneal shunting. Hyperphagia, inertia, adipsia, visual and cognitive impairments can also seriously complicate management. Recurrent cysts may be drained and 90Yttrium or bleomycin instilled. These tumours are commonly aggressive and unsatisfactory to treat when, in most cases, they present early in life.